# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

10/553464

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference SYN 60012/WO | FOR FURTHER ACTION | See Form PCT/IPEA/416 |
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| International application No. PCT/GB2004/001639 | International filing date *(day/month/year)* 15.04.2004 | Priority date *(day/month/year)* 15.04.2003 |
| International Patent Classification (IPC) or national classification and IPC C07C29/42, C07C33/04, C07C31/20, C07C33/044, C07C33/035 | | |
| Applicant JOHNSON MATTHEY PLC et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☐ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 08.11.2004 | 12.09.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Lorenzo Varela, M.J. Telephone No. +49 89 2399-8239 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001639

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-8 as originally filed

   **Claims, Numbers**

   1-5 received on 08.11.2004 with letter of 04.11.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001639

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-5 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-5 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-5 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

D1: WO 02/094741 A (CARREIRA ERICK MORAN ; ADGER BRIAN MICHAEL (GB); ICI PLC (GB)) 28 November 2002 (2002-11-28)

D2: FRANTZ D E ET AL: "FACILE ENANTIOSELECTIVE SYNTHESIS OF PROPARGYLIC ALCOHOLS BY DIRECTADDITION OF TERMINAL ALKYNES TO ALDEHYDES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 122, 1 March 2000 (2000-03-01), pages 1806-1807, XP000931149 ISSN: 0002-7863

D3: BOYALL D ET AL: "Enantioselective addition of 2-methyl-3-butyn-2-ol to aldehydes: preparation of 3-hydroxy-1-butynes" ORGANIC LETTERS, ACS, WASHINGTON, DC, US, vol. 2, no. 26, 28 November 2000 (2000-11-28), pages 4233-4236, XP002207131 ISSN: 1523-7060

D4: BURK M J ET AL: "Highly enantioselective hydrogenation of beta-keto esters under mild conditions" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 117, no. 15, 19 April 1995 (1995-04-19), pages 4423-4424, XP002207132 ISSN: 0002-7863

D5: BACH J ET AL: "Stereoselective Reduction of Unsaturated 1,4-Diketones. A Practical Route to Chiral 1,4-Diols" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 6, 10 February 1997 (1997-02-10), pages 1091-1094, XP004033941 ISSN: 0040-4039

D6: WU K-M ET AL: "Structural effects on Ä1,5Ü-sigmatropic hydrogen shifts of vinylallenes" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 55, no. 14, 6 July 1990 (1990-07-06), pages 4381-4392, XP002207137 ISSN: 0022-3263

D7: US-A-5 110 966 (EVANS JONATHAN C ET AL) 5 May 1992 (1992-05-05)

D8: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1990, XP002289664 retrieved from XFIRE accession no. RID2868854

D9: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1933, XP002289665 retrieved from XFIRE accession no. RID636078

D10: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1962, XP002289666 retrieved from XFIRE accession no. RID1229231

D11: DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1989, XP002289667 retrieved from XFIRE accession no. RID2868243

1. The present application relates to a process for the production of a hydroxyalkyne by coupling reaction between acetaldehyde and a terminal alkyne, comprising the steps of (i) reacting without solvent, a terminal alkyne with a Lewis acidic metal salt: zinc triflate, in the presence of an alkanolamine ligand: (+)- or (-)-N-methylephedrine and a cyclic amine base selected from the group comprising 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo-[4.3.0]non-5-ene and 1,4-diazabicyclo[2.2.2]octane to form a metal-alkyne complex and (ii) adding a solution of acetaldehyde in a solvent selected from a hydrocarbon, aromatic hydrocarbon, ether, alcohol or chlorinated hydrocarbon to the metal-alkyne complex. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction in order to yield a terminal alkyne is reported in the description.

2. D1 relates to a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base. The production of diols using this coupling reaction and possibly a hydrogenation step is disclosed as well. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction to yield a terminal alkyne is reported.

3. D2 relates to a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base.

4. D3 relates to a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction to yield a terminal alkyne is reported.

5. D4 relates to the preparation of phosphorous-containing ligands from saturated diols.

6. D5 relates to the enantioselective hydrogenation of alkyne diols to yield alkene diols and saturated diols.

7. D6 relates to a process for the production of a hydroxyalkyne by reaction of lithium acetylide and an aldehyde.

8. D7 relates to the production of hydroxyalkynes by reaction of a terminal alkyne, a boron derivative and acetaldehyde.

9. D8 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of lithium-diisopropylamid as a base.

10. D9 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of potassium hydroxide, $NaNH_2$ or copper formate.

11. D10 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of magnesium; nBuLi; ethyl bromide and Mg or MeI and Li.

12. D11 relates to a process for the production of a hydroxyalkyne by reaction of acetaldehyde and a terminal alkyne in the presence of nBuLi or ethylmagnesium bromide.

Novelty

13. The subject-matter of claims 1-5 is novel in the sense of Art. 33(2) PCT. None of the available documents of the prior art discloses a process for the production of a hydroxyalkyne by coupling reaction between acetaldehyde and a terminal alkyne, comprising the steps of (i) **reacting without solvent**, a terminal alkyne with a Lewis acidic metal salt in the presence of an alkanolamine ligand and a cyclic amine base to form a metal-alkyne complex and (ii) adding a solution of acetaldehyde to the metal-alkyne complex (see paragraphs 2-12 herein).

Inventive step

14. The subject-matter of claims 1-5 is considered to involve an inventive step in the sense of Art. 33(3) PCT.

a. The closest state of the art, D1 and D3, discloses a process for the production of a hydroxyalkyne by coupling reaction of an aldehyde and a terminal alkyne in the presence of an alkanolamine ligand, a metal triflate and an amine as a base. The production of diols using this coupling reaction and possibly a hydrogenation step is disclosing as well but **the reaction between the terminal alkyne, the alkanolamine, the metal triflate and the amine is carried out in the presence of a solvent.**

b. The problem to be solved in the application can be seen in the provision of an improved process.

c. The problem is solved in the application (see the example and the comparative example) by carrying out the reaction between the terminal alkyne, the alkanolamine, the metal triflate and the amine in the absence of a solvent, leading to higher yield and enantioselectivity (the mention of (+)-N-methylmorpholine instead of (+)-N-methylephedrine in the example is seen as an obvious error-see paragraph 15). Hence, an inventive step is acknowledged.

Further comments

15. Example 2 mentions the use of (+)-N-methylmorpholine instead of (+)-N-methylephedrine as the alkanolamine ligand, leading therefore to lack of clarity, Article 6 PCT. The mention of (+)-N-methylmorpholine is seen as an obvious error due to the following facts: it is not mentioned anywhere else in the specification, it is not an alkanolamine, it is not chiral so the (+) is not possible, the example gives a product with an ee which is impossible without a chiral molecule being present and the weight used in the example 2 does not correspond to 32 mmol of N-methylmorpholine. The compound which should have been mentioned as the alkanolamine is (+)-N-methylephedrine: it is the alkanolamine mentioned in the claims, this alkanolamine is used in the comparative example (carried out in the presence of solvent), it can be a

chiral compound and the weight used in example 2 does correspond to 32 mmol of alkanolamine N-methylephedrine. This error should have been corrected to render the subject-matter of the application clear.

16. There is an inconsistency between the subject-matter of the claims and the description due to the fact that a specific Lewis acidic metal salt: zinc triflate, a specific alkanolamine: (+)/(-)N-methylephedrine, specific cyclic amine bases and specific solvents for the solution of acetaldehyde are mentioned in the main claim 1 whilst alkanolamine in general, a cyclic amine base in general, any solvent for the solution of acetaldehyde and any Lewis acidic metal salt are mentioned in the description as falling within the scope of the application. This scope (mentioned in the description) is broader than justified by the example and an inventive step could not be acknowledged for such a broad generalization from the example. The description should have been brought in accordance with the claims in order to render clear the subject-matter for which protection is sought, Art. 6 PCT.

17. The thermal fragmentation of the hydroxyalkyne obtained in the coupling reaction in order to yield a terminal alkyne is reported in the description. This chemical process as well as example 3, dealing with thermal fragmentation, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.

18. The term "substantially" used at page 4, renders unclear the scope of the protection sought, contrary to Art. 6 PCT.

19. The units of pressure employed in the examples "psi" are not additionally expressed in terms of the units stipulated by Rule 10.1/(a)/and/(b) PCT.

20. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D4 and D5 is not mentioned in the description, nor are these documents identified therein.

Claims

1. A process for performing a coupling reaction between acetaldehyde and a terminal alkyne to yield a hydroxyalkyne comprising the steps of;
   (i) reacting without solvent; a terminal alkyne with zinc triflate in the presence of (+)- or (-)-N-methylephedrine and a cyclic amine base selected from the group comprising 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo-[4.3.0]non-5-ene and 1,4-diazabicyclo[2.2.2]octane, to form a metal-alkyne complex, and
   (ii) adding a solution of acetaldehyde in a solvent selected from a hydrocarbon, aromatic hydrocarbon, ether, alcohol or chlorinated hydrocarbon to the metal-alkyne complex.

2. A process according to claim 1 wherein the terminal alkyne is of general formula $R^1R^2C(OH)C{\equiv}CH$ in which $R^1$ and $R^2$ may be the same or different and are selected from the group comprising methyl, ethyl and propyl.

3. A process according to claim 1 or claim 2 wherein the acetaldehyde concentration is between 0.1 and 2 moles/litre.

4. A process according to any one of claims 1 to 3 wherein step (ii) is performed at –20 to 25°C over a period of 3 to 10 hours.

5. A process according to any one of claims 1 to 4 wherein the molar ratio of zinc triflate : acetaldehyde is 1.5:1, the molar ratio of cyclic amine base: acetaldehyde is 1.6:1 and the molar ratio of (+)- or (-)-N-methylephedrine to acetaldehyde is 1.6:1.